UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,360	01/22/2002	Alexander Steven Whitehead	UPA-008	9510

21323 7590 12/09/2003

TESTA, HURWITZ & THIBEAULT, LLP
HIGH STREET TOWER
125 HIGH STREET
BOSTON, MA 02110

EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 12/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,360	WHITEHEAD, ALEXANDER STEVEN	
	Examiner	Art Unit	
	Jeffrey Fredman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *18,32,34,36,37,41-49,56,57,61 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,19-31,33,35,38-40,50-55 and 58-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-60 and species (1) Inflammatory mediator as TNF alpha, species (2) as SAA1, species (3) as SAA2, species (4) as arthritis and species (5) as steroid in the paper filed October 29, 2003, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). As a result, claims 18, 32, 34, 36, 37, 41-49, 56-57, 61 and 62 are drawn to non elected claims and are withdrawn from prosecution.

The examiner notes that the election is a Markush style election, so that the generic claim will also be examined, and if found allowable, all of the species will be allowed.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 4-6, 8, 9, 11, 19-21, 24, 28, 29-31, 33, 35, 38, 50-55, 58 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Yap et al (J. Am. Soc. Nephrol. (1999) 10:529-537).

Yap teaches a method comprising the steps of claims 1, 4, 5, 6,:

(a) obtaining a body fluid sample from patients undergoing steroid treatment (see page 530, column 1, subheading "Patient population", where a blood sample is taken from children who are on prednisolone)

(b) determining a first level of expression from a first gene known or suspected to be steroid responsive (see page 530, subheading "Semiquantitative reverse Transcription PCR", where genes such as IL-2, IFN-gamma, IL-4 and IL-13 were measured and were suspected of being steroid responsive),

(c) determining a second level of expression of RNA from a second gene known or suspected to be non-responsive to steroids (see page 530, subheading "Semiquantitative reverse Transcription PCR", where cyclophilin was measured and is a housekeeping gene expected to be non-responsive to steroids),

(d) comparing the first and second levels of RNA to create a ratio (see page 530, column 2, where the cytokine index is shown as a ratio of the amount of cytokine RNA divided by the amount of cyclophilin RNA) where the ratio is higher relative to untreated or non-responsive subjects (see page 534, figure 3, where the Nephrotic relapse with steroid result is statistically significantly higher than the patient controls).

With regard to claims 8, 9, 11, Yap teaches RT-PCR amplification of the RNAs (see page 530, subheading "Semiquantitative reverse Transcription PCR").

With regard to claims 19-21, Yap teaches the use of blood and nucleated cells, including T cells (see page 530, column 1).

With regard to claim 24, Yap teaches placement of the blood into a stabilization solution of heparin (see page 530, column 1).

With regard to claim 28, Yap teaches the use of chemokines such as IL-13 (see page 530, column 2).

With regard to claims 29-31, Yap teaches the application of the method to multiple chemokine genes (see page 530, column 2).

With regard to claim 33, Yap teaches application of the method to patients with idiopathic nephrotic syndrome (see abstract).

With regard to claim 35, Yap teaches that the patients may be more or less responsive to steroid treatment (see abstract and page 530 and pages 531-533).

With regard to claim 38, Yap teaches steroid dependent patients (see page 531, column 2, last sentence, for example).

With regard to claims 50-53, Yap teaches measurement of IL-2 (see page 530, column 2, which is a gene controlled by a GRE element (see Bamberger et al (Mol. Cell. Endocrinology, (1997 Dec 31) 136 (1) 23-8, who teach the regulation of IL-2, which is, of course, an inherent property of the molecule).

With regard to claim 54, Yap teaches measurement of cyclophilin (see page 530, subheading "Semiquantitative reverse Transcription PCR", where cyclophilin was measured and is a housekeeping gene expected to be non-responsive to steroids).

With regard to claims 55, 58, Yap teaches administration of prednisolone (see page 530, column 1).

With regard to claim 59, Yap teaches administration orally (see page 530, column 1).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 2, 3, 7, 10, 12-17, 22, 23, 25, 26, 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yap et al (J. Am. Soc. Nephrol. (1999) 10:529-537) as applied to claims 1, 4-6, 8, 9, 11, 19-21, 24, 28, 29-31, 33, 35, 38, 50-55, 58 and 59 above and further in view of Steel et al (Scand. J. Immunol. (1996) 44:493-500).

Yap teaches a method comprising the steps of claims 1, 4, 5, 6,:

(a) obtaining a body fluid sample from patients undergoing steroid treatment (see page 530, column 1, subheading "Patient population", where a blood sample is taken from children who are on prednisolone)

(b) determining a first level of expression from a first gene known or suspected to be steroid responsive (see page 530, subheading "Semiquantitative reverse Transcription PCR", where genes such as IL-2, IFN-gamma, IL-4 and IL-13 were measured and were suspected of being steroid responsive),

(c) determining a second level of expression of RNA from a second gene known or suspected to be non-responsive to steroids (see page 530, subheading "Semiquantitative reverse Transcription PCR", where cyclophilin was measured and is a housekeeping gene expected to be non-responsive to steroids),

(d) comparing the first and second levels of RNA to create a ratio (see page 530, column 2, where the cytokine index is shown as a ratio of the amount of cytokine RNA divided by the amount of cyclophilin RNA) where the ratio is higher relative to untreated or non-responsive subjects (see page 534, figure 3, where the Nephrotic relapse with steroid result is statistically significantly higher than the patient controls, showing differential expression in steroid sensitive patients relative to a normal control).

With regard to claims 8, 9 and 11, Yap teaches RT-PCR amplification of the RNAs (see page 530, subheading "Semiquantitative reverse Transcription PCR").

With regard to claims 19-21, Yap teaches the use of blood and nucleated cells, including T cells (see page 530, column 1).

With regard to claim 24, Yap teaches placement of the blood into a stabilization solution of heparin (see page 530, column 1).

With regard to claim 28, Yap teaches the use of chemokines such as IL-13 (see page 530, column 2).

With regard to claims 29-31, Yap teaches the application of the method to multiple chemokine genes (see page 530, column 2).

With regard to claim 33, Yap teaches application of the method to patients with idiopathic nephrotic syndrome (see abstract).

With regard to claim 35, Yap teaches that the patients may be more or less responsive to steroid treatment (see abstract and page 530 and pages 531-533).

With regard to claim 38, Yap teaches steroid dependent patients (see page 531, column 2, last sentence, for example).

With regard to claims 50-53, Yap teaches measurement of IL-2 (see page 530, column 2, which is a gene controlled by a GRE element (see Bamberger et al (Mol. Cell. Endocrinology, (1997 Dec 31) 136 (1) 23-8, who teach the regulation of IL-2, which is, of course, an inherent property of the molecule).

With regard to claim 54, Yap teaches measurement of cyclophilin (see page 530, subheading "Semiquantitative reverse Transcription PCR", where cyclophilin was measured and is a housekeeping gene expected to be non-responsive to steroids).

With regard to claims 55, 58, Yap teaches administration of prednisolone (see page 530, column 1).

With regard to claim 59, Yap teaches administration orally (see page 530, column 1).

Yap does not teach screening of cells in vitro and does not expressly suggest comparison of pre and post treatment samples as well as the specific genes elected.

Steel teaches a method of claims 2 and 7, comprising the steps:

(a) exposing a cell sample in vitro to a steroid (see page 494, columns 1 and 2).

(b) determining a first level of expression from a first gene known or suspected to be steroid responsive (see page 494, column 2),

(c) determining a second level of expression of RNA from a second gene known or suspected to be non-responsive to steroids (see page 494, column 2),

With regard to claim 3, Steel teaches a comparison of pre and post treatment samples (see figure 4, for example, where a 0 time point represents pre treatment and the 2-72 hour time points represent post treatment samples).

With regard to claim 10, Steel suggests the use of in situ hybridization (see page 498, column 2).

With regard to claim 12, Steel teaches tracking responsiveness over time (see figure 4).

With regard to claims 13-15, Steel teaches induction using inflammatory mediators such as TNFalpha (see page 496, column 1, induction of A-SAA by TNF alpha).

With regard to claims 16-18, Steel teaches administration of interleukins to the cells including a variety of known equivalents (see page 496, column 1).

With regard to claims 26 and 27, Steel teaches analyses of SAA1 and SAA 2 (see page 493, column 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the ratio and method of Yap to measurement of the genes and cell lines of Steel since Yap notes "Cyclophilin was used as the "housekeeping gene" to standardize the amount of cDNA obtained after RT-PCR (see page 531, column 2)". So an ordinary practitioner, reading Yap, would recognize that in analyzing multiple genes for steroid responsiveness, it is important to standardize the results to another gene which remains constant. The ordinary practitioner, applying the method of Yap to the method of Steel, would standardize the results of the SAA1 and SAA2 genes used by Steel by comparing this result to the constitutive SAA gene also disclosed by Steel (see page 493, column 2). The ordinary practitioner would have been motivated to standardize this data because Yap expressly teaches this and because such standardization would reduce sample to sample and patient to patient variability in data based upon extraneous factors such as differences in nucleic acid purification, differences in hybridization efficiency of the gel, array or slide, and different label intensities of the probes on any given test date.

7. Claims 22, 23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yap et al (J. Am. Soc. Nephrol. (1999) 10:529-537) in view of Steel et al (Scand. J. Immunol. (1996) 44:493-500) and further in view of Alkon et al (U.S. Patent 6,300,085).

Yap in view of Steel teach the limitations of claims 1-17, 19-21, 24, 26-31, 33, 35, 38, 50-55, 58 and 59 as discussed above. Yap in view of Steel do not teach the use of Buccal cells, of biopsy samples or of freezing the tissue sample.

Alkon teaches the use of Buccal cells, of biopsy samples or of freezing the tissue sample (see column 13, lines 55-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use any equivalent sample type known in the prior art. Alkon expressly demonstrates the prior art knowledge of the equivalence of blood samples such as those of Yap and buccal or biopsy samples, as well as a variety of methods of storage including freezing the sample. As MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

8. Claims 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yap et al (J. Am. Soc. Nephrol. (1999) 10:529-537) in view of Steel et al (Scand. J. Immunol. (1996) 44:493-500) and further in view of Chikanza et al (Eur. J. Clinical Investigation (1993) 23:845-850).

Yap teaches a method comprising the steps of claims 1, 4, 5, 6,:

(a) obtaining a body fluid sample from patients undergoing steroid treatment (see page 530, column 1, subheading "Patient population", where a blood sample is taken from children who are on prednisolone)

(b) determining a first level of expression from a first gene known or suspected to be steroid responsive (see page 530, subheading "Semiquantitative reverse Transcription PCR", where genes such as IL-2, IFN-gamma, IL-4 and IL-13 were measured and were suspected of being steroid responsive),

(c) determining a second level of expression of RNA from a second gene known or suspected to be non-responsive to steroids (see page 530, subheading "Semiquantitative reverse Transcription PCR", where cyclophilin was measured and is a housekeeping gene expected to be non-responsive to steroids),

(d) comparing the first and second levels of RNA to create a ratio (see page 530, column 2, where the cytokine index is shown as a ratio of the amount of cytokine RNA divided by the amount of cyclophilin RNA) where the ratio is higher relative to untreated or non-responsive subjects (see page 534, figure 3, where the Nephrotic relapse with steroid result is statistically significantly higher than the patient controls, showing differential expression in steroid sensitive patients relative to a normal control).

With regard to claims 8, 9 and 11, Yap teaches RT-PCR amplification of the RNAs (see page 530, subheading "Semiquantitative reverse Transcription PCR").

With regard to claims 19-21, Yap teaches the use of blood and nucleated cells, including T cells (see page 530, column 1).

With regard to claim 24, Yap teaches placement of the blood into a stabilization solution of heparin (see page 530, column 1).

With regard to claim 28, Yap teaches the use of chemokines such as IL-13 (see page 530, column 2).

With regard to claims 29-31, Yap teaches the application of the method to multiple chemokine genes (see page 530, column 2).

With regard to claim 33, Yap teaches application of the method to patients with idiopathic nephrotic syndrome (see abstract).

With regard to claim 35, Yap teaches that the patients may be more or less responsive to steroid treatment (see abstract and page 530 and pages 531-533).

With regard to claim 38, Yap teaches steroid dependent patients (see page 531, column 2, last sentence, for example).

With regard to claims 50-53, Yap teaches measurement of IL-2 (see page 530, column 2, which is a gene controlled by a GRE element (see Bamberger et al (Mol. Cell. Endocrinology, (1997 Dec 31) 136 (1) 23-8, who teach the regulation of IL-2, which is, of course, an inherent property of the molecule).

With regard to claim 54, Yap teaches measurement of cyclophilin (see page 530, subheading "Semiquantitative reverse Transcription PCR", where cyclophilin was measured and is a housekeeping gene expected to be non-responsive to steroids).

With regard to claims 55, 58, Yap teaches administration of prednisolone (see page 530, column 1).

With regard to claim 59, Yap teaches administration orally (see page 530, column 1).

Yap does not teach screening of cells in vitro and does not expressly suggest comparison of pre and post treatment samples as well as the specific genes elected.

Steel teaches a method of claims 2 and 7, comprising the steps:

(a) exposing a cell sample in vitro to a steroid (see page 494, columns 1 and 2).

(b) determining a first level of expression from a first gene known or suspected to be steroid responsive (see page 494, column 2),

(c) determining a second level of expression of RNA from a second gene known or suspected to be non-responsive to steroids (see page 494, column 2),

With regard to claim 3, Steel teaches a comparison of pre and post treatment samples (see figure 4, for example, where a 0 time point represents pre treatment and the 2-72 hour time points represent post treatment samples).

With regard to claim 10, Steel suggests the use of in situ hybridization (see page 498, column 2).

With regard to claim 12, Steel teaches tracking responsiveness over time (see figure 4).

With regard to claims 13-15, Steel teaches induction using inflammatory mediators such as TNFalpha (see page 496, column 1, induction of A-SAA by TNF alpha).

With regard to claims 16-18, Steel teaches administration of interleukins to the cells including a variety of known equivalents (see page 496, column 1).

With regard to claims 26 and 27, Steel teaches analyses of SAA1 and SAA 2 (see page 493, column 1).

Yap in view of Steel do not teach the association of steroid responsiveness with arthritis.

Chikanza teaches the relationship of arthritis to corticosteroid sensitive and resistance (see abstract and pages 847-848, for example).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply steroid analysis method of Yap in view of Steel to measurement in Arthritis since Chikanza states "Since steroid sensitivity and resistance are of undoubted clinical relevance to the steroid therapy of many human diseases, the identification of the SR and SS phenotypes may allow a rational use of corticosteroid dosages. For instance, in the SS subjects, low continuous doses may prove to be more efficacious and possibly less toxic than pulse doses as shown by us (see page 850, column 1)." In fact, Chikanza directly motivates using assays which can differentiate between steroid sensitive and steroid responsive patients in order to perform treatment and an ordinary practitioner, reviewing the art for such methods, would have been led by Yap's statistically significant results to apply Yap's screening method to the motivated use of Chikanza.

As noted previously, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the ratio and method of Yap

to measurement of the genes and cell lines of Steel since Yap notes "Cyclophilin was used as the "housekeeping gene" to standardize the amount of cDNA obtained after RT-PCR (see page 531, column 2)". So an ordinary practitioner, reading Yap, would recognize that in analyzing multiple genes for steroid responsiveness, it is important to standardize the results to another gene which remains constant. The ordinary practitioner, applying the method of Yap to the method of Steel, would standardize the results of the SAA1 and SAA2 genes used by Steel by comparing this result to the constitutive SAA gene also disclosed by Steel (see page 493, column 2). The ordinary practitioner would have been motivated to standardize this data because Yap expressly teaches this and because such standardization would reduce sample to sample and patient to patient variability in data based upon extraneous factors such as differences in nucleic acid purification, differences in hybridization efficiency of the gel, array or slide, and different label intensities of the probes on any given test date.

Allowable Subject Matter

9. The examiner wishes to note that currently it is unclear whether the separate elected species are intended to form a relationship. That is, the claims do not require measurement of SAA1 or SAA2 in arthritis. Claims that were drawn specifically to the ratio of SAA1 to SAA2 as being determinative of the steroid responsive nature of arthritis type conditions would likely overcome the current prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is currently

703-308-6568. In mid January, 2004, when TC 1600 relocates to the new USPTO facility in Alexandria, the examiner's phone number will become 571-272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The supervisor's new telephone number in mid January will be 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is currently 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634